Search Notes
12/19/99
09/103,846

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     FILE 'MEDLINE' ENTERED AT 12:00:03 ON 09 SEP 1999
L1          539 S (MOUSE(W)EMBRYONIC(2A)CELL#)
L2            0 S L1 AND (N(W)ETHYL(W)N(W)NITROSUREA)
L3            1 S L1 AND (METHYLNITROSOUREA)
L4            0 S L1 AND (PROCARBAZINE(A)HYDROCHLORIDE)
L5            0 S L1 AND (TRIETHYLENE MELAMINE)
L6            0 S L1 AND (ACRYLAMIDE MONOMER)
L7            1 S L1 AND (CHLORAMBUCIL)
L8            2 S L1 AND (MELPHALAN)
L9            0 S L1 AND (CYCLOPHOSPHAMIDE)
L10           0 S L1 AND (DIETHYL SULFATE)
L11           0 S L1 AND (ETHYL METHANE SULFONATE)
L12           0 S L1 AND (METHYL METHANE SULFONATE)
L13           0 S L1 AND (6(W)MERCAPTOPURINE)
L14           2 S L1 AND (MITOMYCIN(W)C)
L15           2 S L1 AND (N(W)METHYL(W)N(W)NITRO(W)N(W)NITROSOGUANIDINE)
L16           0 S L1 AND (3(W)H(W)2(W)O)
L17           0 S L1 AND (IRETJAME)
L18           1 S L1 AND (URETHANE)
L19           2 S L1 AND (ULTRAVIOLET LIGHT)
L20          26 S L1 AND (X(W)RAY OR RADIATION)
L21           7 S L1 AND (MISMATCH OR STRAND BREAK)
                E WOYCHIK R P/AU
L22          57 S E3
L23           2 S L22 AND MODIFI?
                E D

L23 1 AB
L24           0 S L22 AND (TARGET CELL#)
L25           0 S L22 AND (MISMATCH OR STRAND BREAK)
L26          20 S L22 AND (MUTATION)
L27           0 S L26 AND (EMBRYONIC STEM CELL#)
L28           0 S L26 AND (EMBRYONIC STEM(2A)CELL#)
L29           0 S L22 AND (EMBRYONIC STEM(2A)CELL#)
                E MAGNUSON T R/AU
L30           4 S E3
                E AVNER E D/AU
L31          88 S E2-E3
L32          10 S L31 AND (MUTATION#)
L33          78 S L31 NOT L32
L34           0 S L33 AND (MISMATCH## OR STRAND(W)BREAK#)
L35           4 S L33 AND (EMBRYONIC)

     FILE 'BIOSIS, CAPLUS, EMBASE' ENTERED AT 13:25:55 ON 09 SEP 1999
L36           0 S L2
L37           0 S L4
L38           6 S L9
L39           4 DUP REM L38 (2 DUPLICATES REMOVED)
L40           0 S L10
L41           0 S L11
L42           0 S L12
L43           0 S L13
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STIC-ILL

From: Martin, Jill
Sent: Thursday, September 09, 1999 12:11 PM
To: STIC-ILL
Subject: REF

Jill Martin
305-2147
PCT/US99/14216
Thanks!

L7 ANSWER 1 OF 1 MEDLINE
AN 1998400236 MEDLINE
DN 98400236
TI Mammalian 3-methyladenine DNA glycosylase protects against the toxicity and clastogenicity of certain chemotherapeutic DNA cross-linking agents.
AU Allan J M; Engelward B P; Dreslin A J; Wyatt M D; Tomasz M; Samson L D
CS Department of Cancer Cell Biology, Harvard School of Public Health, Boston, Massachusetts 02115, USA.
NC RO1 CA55042 (NCI)
RO1CA28681 (NCI)
CA73135-01 (NCI)
+
SO CANCER RESEARCH, (1998 Sep 1) 58 (17) 3965-73.
Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199811
EW 19981103

=> D L7 AB

L7 ANSWER 1 OF 1 MEDLINE
AB DNA repair status is recognized as an important determinant of the clinical efficacy of cancer chemotherapy. To assess the role that a mammalian DNA glycosylase plays in modulating the toxicity and clastogenicity of the chemotherapeutic DNA cross-linking alkylating agents, we compared the sensitivity of wild-type murine cells to that of isogenic cells bearing homozygous null mutations in the 3-methyladenine DNA glycosylase gene (Aag). We show that Aag protects against the toxic and clastogenic effects of 1,3-bis(2-chloroethyl)-1-nitrosourea and mitomycin C (MMC), as measured by cell killing, sister chromatid exchange, and chromosome aberrations. This protection is accompanied by suppression of apoptosis and a slightly reduced p53 response. Our results identify 3-methyladenine DNA glycosylase-initiated base excision repair as a potentially important determinant of the clinical efficacy and, possibly, the carcinogenicity of these widely used chemotherapeutic agents. However, Aag does not contribute significantly to protection against the toxic and clastogenic effects of several chemotherapeutic nitrogen mustards (namely, mechlorethamine, melphalan, and ***chlorambucil***), at least in the ***mouse*** ***embryonic*** stem ***cells*** used here. We also compare the Aag null phenotype with the Fanconi anemia phenotype, a human disorder characterized by cellular hypersensitivity to DNA cross-linking agents, including MMC. Although Aag null cells are sensitive to

STIC-ILL

From: Martin, Jill
Sent: Thursday, September 09, 1999 12:07 PM
T : STIC-ILL
Subject: REF

Jill Martin
305-2147
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Thanks!

L3 ANSWER 1 OF 1 MEDLINE
AN 97306204 MEDLINE
DN 97306204
TI Alkylation-induced apoptosis of embryonic stem cells in which the gene for DNA-repair, methyltransferase, had been disrupted by gene targeting.
AU Tominaga Y; Tsuzuki T; Shiraishi A; Kawate H; Sekiguchi M
CS Department of Biochemistry, Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan.
SO CARCINOGENESIS, (1997 May) 18 (5) 889-96.
Journal code: C9T. ISSN: 0143-3334.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199708

=> d l3 ab

L3 ANSWER 1 OF 1 MEDLINE
AB An enzyme O6-methylguanine-DNA methyltransferase (MGMT) catalyzes transfer of a methyl group from O6-methylguanine and O4-methylthymine of alkylated DNA to its own molecule, thereby repairing the pre-mutagenic lesions in a single step reaction. Making use of gene targeting, we developed ***mouse*** ***embryonic*** stem (ES) ***cell*** lines deficient in the methyltransferase. Quantitative immunoblot analysis and enzyme assay revealed that MGMT-/- cells, in which both alleles were disrupted, contained no methyltransferase protein while cells with one intact allele (MGMT+/-) contained about half the amount of protein carried by the parental MGMT+/+ cells. MGMT-/- cells have an extremely high degree of sensitivity to simple alkylating agents, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and N-methyl-N-nitrosourea (MNU), whereas MGMT+/- cells are slightly more sensitive to these agents, as compared with findings from normal cells. A high frequency of mutation was induced in MGMT-/- cells on exposure to a relatively low dose of MNNG. Electrophoretic analyses of the DNAs as well as fluorochrome staining of the cells revealed that MGMT-/- cells treated with MNNG undergo apoptotic death, which occurs after G2-M arrest in the second cycle of cell proliferation.

Jill Martin
Art Unit 1632

STIC-ILL

From: Martin, Jill
Sent: Thursday, September 09, 1999 12:47 PM
T : STIC-ILL
Subject: REF

Jill Martin
305-2147
PCT/US99/14216
Thanks!!

L20 ANSWER 7 OF 26 MEDLINE
AN 1998369178 MEDLINE
DN 98369178
TI BRCA1 required for transcription-coupled repair of oxidative DNA damage.
AU Gowen L C; Avrutskaya A V; Latour A M; Koller B H; Leadon S A
CS Curriculum in Genetics and Molecular Biology and Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.
NC CA70490 (NCI)
IP50CA58223 (NCI)
CA40453 (NCI)
SO SCIENCE, (1998 Aug 14) 281 (5379) 1009-12.
Journal code: UJ7. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199810
EW 19981005

L20 ANSWER 7 OF 26 MEDLINE
AB The breast and ovarian cancer susceptibility gene BRCA1 encodes a zinc finger protein of unknown function. Association of the BRCA1 protein with the DNA repair protein Rad51 and changes in the phosphorylation and cellular localization of the protein after exposure to DNA-damaging agents are consistent with a role for BRCA1 in DNA repair. Here, it is shown that ***mouse*** ***embryonic*** stem ***cells*** deficient in BRCA1 are defective in the ability to carry out transcription-coupled repair of oxidative DNA damage, and are hypersensitive to ionizing ***radiation*** and hydrogen peroxide. These results suggest that BRCA1 participates, directly or indirectly, in transcription-coupled repair of oxidative DNA damage.

Jill Martin
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STIC-ILL

From: Martin, Jill
Sent: Thursday, September 09, 1999 12:16 PM
To: STIC-ILL
Subject: REF

Jill Martin
305-2147
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Thanks!

L14 ANSWER 2 OF 2 MEDLINE
AN 95408305 MEDLINE
DN 95408305
TI Gene targeting of DT-diaphorase in ***mouse*** ***embryonic*** stem ***cells*** : establishment of null mutant and its ***mitomycin*** ***C*** -resistance.
AU Yoshida T; Tsuda H
CS Life Science Research Laboratory, Japan Tobacco Inc., Kanagawa..
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1995 Sep 14) 214 (2) 701-8.
Journal code: 9Y8. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199512

=> D
L14 2 AB

L14 ANSWER 2 OF 2 MEDLINE
AB It is generally accepted that DT-diaphorase is primarily involved in the detoxification of quinone compounds and is capable of metabolically activating some cancer chemotherapeutic quinones including ***mitomycin*** ***C*** . However, these conclusions have mainly been drawn from the experiments using the DT-diaphorase inhibitor, dicoumarol. To understand directly the roles of this enzyme in quinone metabolism, we have established heterozygously and homozygously DT-diaphorase-targeted mutant embryonic stem (ES) cells by homologous recombination. Cytotoxicity experiments using these cells clearly demonstrated that DT-diaphorase acts as an activator of ***mitomycin*** ***C*** in ES cells. These mutant cell lines seem to be very useful for investigating the functions of DT-diaphorase including the bioactivation and detoxification of quinone species. The generation of a DT-diaphorase-targeted mouse is under investigation.

Jill Martin
Art Unit 1632

STIC-ILL 09/963,735

Fr m: Martin, Jill
Sent: Thursday, September 09, 1999 1:34 PM
T : STIC-ILL
Subject: REF

Jill Martin
305-2147
PCT/US99/14216
Thanks!

L39 ANSWER 2 OF 4 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 1
AN 1996:298654 CAPLUS
DN 124:335031
TI The stem-cell test: an in vitro assay for teratogenic potential. Results of a blind trial with 25 compounds
AU Newall, D. R.; Beedles, K. E.
CS Genetic and Reproductive Toxicology, Glaxo Wellcome Research and Development, Ware, Herts, SG12 0DP, UK
SO Toxicol. in Vitro (1996), 10(2), 229-240
CODEN: TIVIEQ; ISSN: 0887-2333
DT Journal
LA L39 ANSWER 3 OF 4 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 2
AB The stem-cell test is a novel assay for teratogenic potential which uses a propagated cell line. ***Mouse*** ***embryonic*** stem ***cells*** (ESC) are maintained in an undifferentiated state in the presence of leukemia inhibitory factor (LIF). On removing LIF, the cells differentiate into an embryonic endoderm that is morphol. distinct from ESC. Colonies of ESC are maintained from which cells can be harvested daily, and these cells, when washed free of LIF, form a population of differentiating cells on which the effects of chems. can be tested. The conditions under which differentiating ESC can be substituted for rat primary embryonic cells in a micromass test protocol have been detd., and the effects of 25 compds. investigated in a blind trial. The stem-cell test predicted the teratogenicity of these compds. with a similar sensitivity and specificity to the micromass test, with the advantage that the test uses a propagated cell line; there is no use of animals.

Jill Martin
Art Unit 1632

12
1632-AM
9-13-RC

STIC-ILL

From: Martin, Jill
Sent: Thursday, September 09, 1999 12:13 PM
To: STIC-ILL
Subject: REF

Jill Martin
305-2147
PCT/US99/14216
Thanks!

L8 ANSWER 2 OF 2 MEDLINE
AN 97415542 MEDLINE
DN 97415542
TI Enhanced apoptosis in metallothionein null cells.
AU Kondo Y; Rusnak J M; Hoyt D G; Settineri C E; Pitt B R; Lazo J S
CS Department of Pharmacology, University of Pittsburgh, Pennsylvania 15261, USA.
NC CA61299 (NCI)
DK46935 (NIDDK)
HL32154 (NHLBI)
SO MOLECULAR PHARMACOLOGY, (1997 Aug) 52 (2) 195-201.
Journal code: NGR. ISSN: 0026-895X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199711

=> D
L8 2 AB

L8 ANSWER 2 OF 2 MEDLINE
AB Metallothioneins (MTs) are major intracellular, zinc-binding proteins with antioxidant properties. ***Mouse*** ***embryonic*** ***cells*** null for MT due to loss of functional MT I and II genes (MT-/-) were more susceptible to apoptotic death after exposure to tert-butyl hydroperoxide or the anti-cancer agents cytosine arabinoside, bleomycin, ***melphalan*** , and cis-dichlorodiammineplatinum(II) compared with wild-type ***mouse*** ***embryonic*** ***cells*** (MT+/+). We measured basal levels of the tumor suppressor protein p53 and the death effector protein Bax and found the basal levels of both proteins were higher in MT null cells compared with MT+/+ cells. After treatment with the DNA-damaging agent cis-dichlorodiammineplatinum(II), p53 protein levels were induced in both MT+/+ and MT-/- cells with MT null cells always maintaining the highest p53 levels. The elevated sensitivity to apoptosis was not restricted to embryonic cells. Primary pulmonary fibroblasts were isolated from distinct litters of MT null, heterozygous, and wild-type mice, and all had undetectable basal MT levels. Zinc exposure increased MT levels in the wild-type and heterozygous fibroblasts but not in the MT null fibroblasts. Consistent with the induced MT levels, we found MT+/+ and MT+/- embryonic cells were less sensitive to cis-dichlorodiammineplatinum(II)-induced apoptosis compared with MT-/- cells. Our results implicate MT as a stress-responsive factor that can regulate apoptotic engagement.

STIC-ILL

From: Martin, Jill
Sent: Thursday, September 09, 1999 1:06 PM
T : STIC-ILL
Subject: REF

Jill Martin
305-2147
PCT/US99/14216
Thanks!!

6 ANSWER 20 OF 20 MEDLINE
AN 86040459 MEDLINE
DN 86040459
TI An inherited limb deformity created by insertional mutagenesis in a transgenic mouse.
AU ***Woychik R P*** ; Stewart T A; Davis L G; D'Eustachio P; Leder P
SO NATURE, (1985 Nov 7-13) 318 (6041) 36-40.
Journal code: NSC. ISSN: 0028-0836.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 198602

=> D
L26 20 AB

L26 ANSWER 20 OF 20 MEDLINE
AB We have created an insertional ***mutation*** that leads to a severe defect in the pattern of limb formation in the developing mouse. The novel recessive ***mutation*** is phenotypically identical and non-complementary to two previously encountered limb deformity mutations, and is closely linked to a dominant ***mutation*** that gives rise to a related limb dysmorphism. The inserted element thus provides a molecular genetic link with the control of pattern formation in the mammalian embryo.

Jill Martin
Art Unit 1632

STIC-ILL

From: Martin, Jill
Sent: Thursday, September 09, 1999 1:14 PM
To: STIC-ILL
Subject: REF

Jill Martin
305-2147
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Thanks!!

L26 ANSWER 4 OF 20 MEDLINE
AN 95402699 MEDLINE
DN 95402699
TI Molecular and phenotypic characterization of a new mouse insertional ***mutation*** that causes a defect in the distal vertebrae of the spine.
AU Schrick J J; Dickinson M E; Hogan B L; Selby P B; ***Woychik R P***
CS University of Tennessee, Graduate School for Biomedical Sciences, Oak Ridge 37831-8080, USA.
NC RO1 HD-25323 (NICHD)
SO GENETICS, (1995 Jul) 140 (3) 1061-7.
Journal code: FNH. ISSN: 0016-6731.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EL26 ANSWER 4 OF 20 MEDLINE
AB We have identified and characterized the phenotype of a new insertional ***mutation*** in one line of transgenic mice. Mice carrying this ***mutation*** , which we have designated TgN(Imusd)370Rpw, display undulations of the vertebrae giving rise to a novel kinky-tail phenotype. Molecular characterization of the insertion site indicates that the transgene integration has occurred without any substantial alterations in the structure of the host sequences. Using probes that flank the insertion site, we have mapped the ***mutation*** to chromosome 5 near the semidominant ***mutation*** , thick tail (Tht). Thick tail does not complement the TgN(Imusd)370Rpw ***mutation*** ; compound mutants containing one copy of each ***mutation*** display a more severe phenotype than either ***mutation*** individually.

Jill Martin
Art Unit 1632

963,737

STIC-ILL

From: Martin, Jill
Sent: Thursday, September 09, 1999 12:20 PM
T : STIC-ILL
Subject: REF

Jill Martin
305-2147
PCT/US99/14216
Thanks!

ZGE-990913 8008

L15 ANSWER 1 OF 2 MEDLINE
AN 1998408012 MEDLINE
DN 98408012
TI Protein synthesis and transcriptional inhibitors control ***N*** - ***methyl*** - ***N*** '- ***nitro*** - ***N*** - ***nitrosoguanidine*** -induced levels of APC mRNA in a p53-dependent manner.
AU Jaiswal A S; Narayan S
CS Sealy Center for Oncology and Hematology, University of Texas Medical Branch, Galveston, TX 77555-1048, USA.
SO INTERNATIONAL JOURNAL OF ONCOLOGY, (1998 Oct) 13 (4) 733-40. Journal code: CX5. ISSN: 1019-6439.
CY Greece
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199902
EW 19990204

L15 ANSWER 1 OF 2 MEDLINE
AB In the present study, we show that treatment of wild-type (p53+/+) ***mouse*** ***embryonic*** fibroblast (MEF) ***cells*** with a DNA-alkylating agent, N-methyl-N'-nitro-N-nitro-soguanidine (MNNG), resulted in increased levels of adenomatous polyposis coli (APC) mRNA compared to p53 gene-knocked out (p53-/-) MEF cells, indicating that p53 is required for APC expression after alkylation damage. By using HCT-116 colon cancer cells (containing wild-type p53 gene) or p53-/- MEF cells transfected with a pCMV-p53 overexpression plasmid [p53-/-(CMV-p53)], we show that p53 is a labile factor for APC gene expression, and that pretreating HCT-116 cells with a protein synthesis inhibitor, cycloheximide (CHX), inhibited MNNG-induced APC mRNA levels by inhibiting p53 protein synthesis. The effect of CHX on p53 protein synthesis was reversible, as the withdrawal of CHX permitted p53 protein synthesis to resume with a concomitant increase in APC mRNA levels after MNNG treatment. To examine whether p53 regulates APC gene expression at the transcriptional level, we treated HCT-116 or p53-/-(CMV-p53) MEF cells with 5,6-dichloro-1-beta-D-ribofuranosylbenzamidazole (DRB; a transcriptional inhibitor), before the MNNG treatment. Although treatment of cells with DRB resulted in increased p53 protein levels, that the APC mRNA levels were decreased suggests that p53 may enhance APC gene expression upstream of the transcriptional machinery where DRB interacts. That the withdrawal of DRB, and subsequent MNNG treatment, increased the level of APC mRNA indicated that the binding of DRB to the transcriptional machinery was reversible.

Jill Martin

263677

STIC-ILL

Fr m: Martin, Jill
Sent: Thursday, September 09, 1999 1:16 PM
T : STIC-ILL
Subject: REF

Jill Martin
305-2147
PCT/US99/14216
Thanks!!

9909091636

L26 ANSWER 3 OF 20 MEDLINE
AN 96187435 MEDLINE
DN 96187435
TI Insertional mutagenesis and molecular analysis of a new gene associated with polycystic kidney disease.
AU Yoder B K; Richards W G; Sweeney W E; Wilkinson J E; Avener E D; ***Woychik R P***
CS Biology Division, Oak Ridge National Laboratory, TN 37831-8080, USA.
NC 1 RO1 DK45633-01 (NIDDK)
5 RO1 DK44875 (NIDDK)
SO PROCEEDINGS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, (1995 Oct) 107 (3) 314-23.
Journal code: CDQ. ISSN: 1081-650X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
E
L26 ANSWER 3 OF 20 MEDLINE
AB We have identified a new insertional ***mutation*** in the mouse (TgN737Rpw) that causes a phenotype that closely resembles human autosomal recessive polycystic kidney disease. The renal pathology in these mutants first presents itself as a dilation of the proximal tubules, which is quickly followed by the development of cystic lesions in the collecting ducts. The livers in the mutant animals develop a variable lesion depending upon the genetic background. We have cloned the mutant locus and have isolated and characterized a gene, Tg737, whose expression is disrupted in the mutant animals. Expression of the Tg737 gene can normally be detected using the Northern blot analysis at low levels in a variety of tissues, including the kidney and liver. Using the in situ hybridization procedure, expression of the Tg737 mRNA can be detected in the collecting ducts of adult kidneys and in portions of the embryonic day 15.5 kidney. Most important, we have corrected the defective kidney trait by expressing the wild-type cDNA as a transgene in the mutant animals. The human homologue of the Tg737 gene has also been cloned and mapped to human chromosome 13.

9/9
ND

Jill Martin
Art Unit 1632

STIC-ILL

From: Martin, Jill
Sent: Thursday, September 09, 1999 12:20 PM
To: STIC-ILL
Subject: REF

Jill Martin
305-2147
PCT/US99/14216
Thanks!

L15 ANSWER 2 OF 2 MEDLINE
AN 97306204 MEDLINE
DN 97306204
TI Alkylation-induced apoptosis of embryonic stem cells in which the gene for DNA-repair, methyltransferase, had been disrupted by gene targeting.
AU Tominaga Y; Tsuzuki T; Shiraishi A; Kawate H; Sekiguchi M
CS Department of Biochemistry, Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan.
SO CARCINOGENESIS, (1997 May) 18 (5) 889-96.
Journal code: C9T. ISSN: 0143-3334.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199708
L15 ANSWER 2 OF 2 MEDLINE
AB An enzyme O6-methylguanine-DNA methyltransferase (MGMT) catalyzes transfer of a methyl group from O6-methylguanine and O4-methylthymine of alkylated DNA to its own molecule, thereby repairing the pre-mutagenic lesions in a single step reaction. Making use of gene targeting, we developed ***mouse*** ***embryonic*** stem (ES) ***cell*** lines deficient in the methyltransferase. Quantitative immunoblot analysis and enzyme assay revealed that MGMT-/- cells, in which both alleles were disrupted, contained no methyltransferase protein while cells with one intact allele (MGMT+/-) contained about half the amount of protein carried by the parental MGMT+/+ cells. MGMT-/- cells have an extremely high degree of sensitivity to simple alkylating agents, ***N*** - ***methyl*** - ***N*** '- ***nitro*** - ***N*** - ***nitrosoguanidine*** (MNNG) and N-methyl-N-nitrosourea (MNU), whereas MGMT+/- cells are slightly more sensitive to these agents, as compared with findings from normal cells. A high frequency of mutation was induced in MGMT-/- cells on exposure to a relatively low dose of MNNG. Electrophoretic analyses of the DNAs as well as fluorochrome staining of the cells revealed that MGMT-/- cells treated with MNNG undergo apoptotic death, which occurs after G2-M arrest in the second cycle of cell proliferation.

Jill Martin
Art Unit 1632

STIC-ILL

From: Martin, Jill
Sent: Thursday, September 09, 1999 12:33 PM
To: STIC-ILL
Subject: REF

Jill Martin
305-2147
PCT/US99/14216
Thanks!

L19 ANSWER 1 OF 2 MEDLINE
AN 97220036 MEDLINE
DN 97220036
TI Characterization of defective nucleotide excision repair in XPC mutant mice.
AU Cheo D L; Ruven H J; Meira L B; Hammer R E; Burns D K; Tappe N J; van Zeeland A A; Mullenders L H; Friedberg E C
CS Department of Pathology, The University of Texas Southwestern Medical Center, Dallas 75235, USA.
NC CA44247 (NCI)
SO MUTATION RESEARCH, (1997 Mar 4) 374 (1) 1-9.
Journal code: NNA. ISSN: 0027-5107.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199706
EL19 ANSWER 1 OF 2 MEDLINE
AB Nucleotide excision repair (NER) is a fundamental process required for maintaining the integrity of the genome in cells exposed to environmental DNA damage. Humans defective in NER suffer from the hereditary cancer-prone disease xeroderma pigmentosum. In order to model this disease in mice a mutation in the mouse XPC gene was generated and used to replace a wild-type XPC allele in ***mouse*** ***embryonic*** stem ***cells*** by homologous recombination. These cells were used to derive XPC mutant mice. Fibroblasts from mutant embryos were more sensitive to the cytotoxic effects of ***ultraviolet*** ***light*** than wild-type and heterozygous cells. Repair synthesis of DNA following irradiation with ***ultraviolet*** ***light*** was reduced in these cells, indicating a defect in NER. Additionally, XPC mutant embryo fibroblasts were specifically defective in the removal of pyrimidine (6-4) pyrimidone photoproducts from the non-transcribed strand of the transcriptionally active p53 gene. Mice defective in the XPC gene appear to be an excellent model for studying the role of NER and its interaction with other proteins in the molecular pathogenesis of cancer in mammals following exposure to environmental carcinogens.

Jill Martin
Art Unit 1632

STIC-ILL

From: Martin, Jill
Sent: Thursday, September 09, 1999 12:34 PM
To: STIC-ILL
Subject: REF

Jill Martin
305-2147
PCT/US99/14216
Thanks!

L19 ANSWER 2 OF 2 MEDLINE
AN 97194977 MEDLINE
DN 97194977
TI Quantification of XPA gene expression levels in human and mouse cell lines by competitive RT-PCR.
AU Layher S K; Cleaver J E
CS Laboratory of Radiobiology and Environmental Health, University of California, San Francisco 94143-0750, USA.
NC 5 T32 ES07106 (NIEHS)
SO MUTATION RESEARCH, (1997 Jan 31) 383 (1) 9-19.
Journal code: NNA. ISSN: 0027-5107.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199705
EW 19970504

L19 ANSWER 2 OF 2 MEDLINE
AB Expression of the mammalian photoproduct-specific DNA-binding protein XPA has been quantified by competitive reverse transcription-polymerase chain reaction, a method that provides relative numbers of mRNA molecules per cell. Human primary and simian virus (SV)40-transformed fibroblasts had 4.8 and 8.4 transcripts per ***cell*** , respectively; ***mouse*** ***embryonic*** and SV40-transformed fibroblasts had 6.7 and 5.5 transcripts per cell, respectively. None of these differences are significant, and the mean value of 5 to 8 transcripts per cell indicates that XPA is expressed as a low-abundance mRNA. Two cell lines transfected with XPA on a conditional promoter showed different numbers of XPA mRNA molecules, consistent with their respective responses to an inducer and their sensitivity to ***ultraviolet*** ***light*** . The similarity of results in human and mouse cells shows that a difference in XPA expression cannot account for the greater repair of nontranscribed DNA in human cells.

Jill Martin
Art Unit 1632

STIC-ILL

From: Martin, Jill
Sent: Thursday, September 09, 1999 1:33 PM
T : STIC-ILL
Subject: REF

Jill Martin
305-2147
PCT/US99/14216
Thanks!

L39 ANSWER 3 OF 4 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 2
AN 1994:648154 CAPLUS
DN 121:248154
TI The stem-cell test - a novel in vitro assay for teratogenic potential
AU Newall, D. R.; Beedles, K. E.
CS Genetic and Reproductive Toxicology, Glaxo Group Research Ltd., Herts, SG12 ODP, UK
SO Toxicol. in Vitro (1994), 8(4), 697-701
CODEN: TIVIEQ; ISSN: 0887-2333
DT Journal
LA English

L39 ANSWER 3 OF 4 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 2
AB The stem-cell test is a novel assay for teratogenic potential which uses a propagated cell line. ***Mouse*** ***embryonic*** stem ***cells*** (ESC) are maintained in an undifferentiated state in the presence of leukemia inhibitory factor (LIF). On removing LIF, the cells differentiate into an embryonic endoderm that is morphol. distinct from ESC. Colonies of ESC are maintained from which cells can be harvested daily, and these cells, when washed free of LIF, form a population of differentiating cells on which the effects of chems. can be tested. The conditions under which differentiating ESC can be substituted for rat primary embryonic cells in a micromass test protocol have been detd., and the effects of 25 compds. investigated in a blind trial. The stem-cell test predicted the teratogenicity of these compds. with a similar sensitivity and specificity to the micromass test, with the advantage that the test uses a propagated cell line; there is no use of animals.

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